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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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DAVID S. RESNICK
100 SUMMER STREET
NIXON PEABODY LLP
BOSTON, MA 02110-2131

EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/726,422	ZETTER ET AL.	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-16 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/3/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-5, 17 and 20, drawn to an antibody or fragment thereof, which selectively binds human thymosin β15, and methods of use thereof, classified in class 530, subclass 387.1.

II. Claims 6 and 7, drawn to a polypeptide comprising the sequence of SEQ ID NO: 2, and fragments thereof, classified in class 530, subclass 350.

III. Claims 8-16, drawn to polynucleotides encoding human thymosin β15, and fragments, vectors, and host cells thereof, classified in class 536, subclass 23.1.

IV. Claim 17-19, and 21, drawn to antisense compounds directed to human thymosin β15, and methods of use thereof, classified in class 514, subclass 44.

The inventions are distinct, each from the other because of the following reasons:

The inventions of Groups I-IV are directed to related compounds and their methods of use. The related inventions are distinct if the inventions as claimed do not overlap in scope, i.e., are mutually exclusive; the inventions as claimed are not obvious variants; and the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect. See MPEP § 806.05(j). In the instant case, the inventions as claimed do not overlap in scope, since each Group is directed to the use of a different compound, none of which share a common core structure. Because the inventions as claimed are not obvious variants for the same reason, and have at least materially different designs and modes of operation, the inventions are accordingly considered distinct. Furthermore, since the search for

the compounds of each distinct group require the use of different keywords, and because the art returned by the searches are divergent and non-coextensive, it is considered a serious burden upon the examiner to search and examine each group in a single application. Restriction is proper therefore.

Claim 17 link(s) inventions I and IV. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claim17. Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104 Claims that require all the limitations of an allowable linking claim will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Applicant(s) are advised that if any claim(s) including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. In re Ziegler, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

During a telephone conversation with Leena Khartounen on 6 March 2006 a provisional election was made without traverse to prosecute the invention of Group IV, claims 17-19 and 21. Affirmation of this election must be made by applicant in replying to this Office action. Claims

1-16, and 20 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The disclosure contains sequences which fall under the purview of 37 CFR 1.821 through 1.825 as requiring SEQ ID NOS:, but which are not so identified. For example, the drawings of the instant specification contain at least one sequence in excess of 10 nucleotides long, for example in figure 3, which are not identified by a SEQ ID NO:. Applicants should be aware that this sequence may not be the only instance necessitating this notice. Applicants should carefully review the application for any further examples of failures to identify any sequences by SEQ ID NO:, and to otherwise verify that the application is in compliance. A complete reply to the instant Official action must cure these defects, as this requirement will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of suppressing the activity or production of the human thymosin B15, does not reasonably provide enablement for *in vivo* suppression of the activity or production of the human thymosin B15 in whole animals. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The invention of the above listed claims is drawn to methods of treating neoplastic cells expressing human thymosin B15 comprising administering to a cell an effective amount of a compound which suppresses the activity or production of the human thymosin B15, whereby the compound may be an antisense oligonucleotide. The specification teaches a method of using thymosin B15-specific polyclonal antibodies to inhibit the expression of thymosin B15 *in vitro*.

The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of using the compounds in *in vivo* environments. The specification also fails to give meaningful guidance as to how neoplastic cells may be treated. Additionally, a person skilled in the art would recognize that predicting the treatment of neoplastic cells using an antisense compound *in vivo* based solely on the performance of an unrelated compound *in vitro* is highly problematic. Thus, although the specification prophetically

considers and discloses general methodologies of treating neoplastic cells *in vivo*, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable.

The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The specification broadly claims to provide for treatment of cancerous cells. The specification does not disclose any working examples of said treatment, and otherwise supplies only prophetic guidance for direction. In light of the lack of clear guidance from the specification for how to such cancerous cells, determination of enablement depends heavily upon the state of the prior art for support. However, as described below, the state of the art of treating cancer by successfully using antisense-mediated therapies as contemplated is unpredictable.

The following references are cited herein to illustrate the state of the art of antibody- and antisense-mediated treatment.

A recent (2002) article by Braasch et al. opens by emphasizing that major obstacles persist in the antisense therapy art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable

efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the

potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism" (Pg. 4503, para. 1 and 2). Branch affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column). Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

Thus, the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in*

vitro experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above.

Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of thymosin B15 *in vitro* using an antibody as being correlative or representative of the successful *in vivo* use of antisense compounds in the treatment of neoplastic conditions suspected of being associated with thymosin B15 expression. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antisense-mediated treatment or prevention of any conditions or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by such compounds.

Since the specification fails to provide any guidance for the successful treatment of neoplastic conditions other than in cells *in vitro*, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable as outlined above, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation as presented in the specification over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 21 is rejected under 35 U.S.C. 102(b) as being anticipated by Abrams et al. (WO 94/12639).

The invention of the above claim is drawn to an isolated nucleotide segment of at least 10 nucleotides which hybridizes under stringent conditions to DNA fragment of SEQ ID NO:1.

Nucleotides 2-31 of SEQ ID NO:374 of Abrams et al. is 80% identical to the complement of nucleotides 181-210 of the instant SEQ ID NO: 1. In the lack of evidence to the contrary, SEQ ID NO: 374 of Abrams et al. would thus be considered to hybridize to a DNA fragment having a sequence set forth in SEQ ID NO: 1. Abrams et al. is thus considered to teach all the claim limitations of the instant claim 21, and anticipates it therefore.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 21 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 10 of U.S. Patent No. 5,663,071. Although the conflicting claims are not identical, they are not patentably distinct from each other because

claim 10 of U.S. Patent Number 5,663,071 is drawn to an isolated nucleotide segment which comprises 30 to 50 nucleotides and hybridizes under stringent conditions to a DNA fragment having the nucleotide sequence set forth in SEQ ID NO: 1, while the instant claim 21 is drawn to an isolated nucleotide segment comprising at least 10 nucleotides and hybridizes under stringent conditions to a DNA fragment having the nucleotide sequences set forth in SEQ ID NO:1. Claim 10 of U.S. Patent Number 5,663,071 therefore anticipates the instant claim 21.

Conclusion

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables

applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JDS

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER